Advances in Allergy & Asthma, 2013-2015

Montana Asthma Advisory Group Meeting

15 May 2015

Advances on many fronts

- Asthma mechanisms
- Cell mechanisms of cytokines and interleukins
- Medications targeted to cell functions
- Practice Parameters
- Allergy and its impact on asthma
- Atopic dermatitis and food allergy
- Environmental assessment and control
- Teaching techniques and approaches
- Efforts to improve adherence

Asthma mechanisms

- Announcement of a Calcium sensing receptor discovery in asthmatics by Mayo Clinic April 22, 2015
- Asthmatics have high extracellular calcium
- Claims for a cure within 5 years may be premature

- Hygiene Hypothesis shift from Th1to Th2 cells which produce Interleukins (i.e., IL-4, 5, 6, and 13).
- This leads to increased levels of allergy by increased production of immunoglobulin E (IgE).
- Interleukins are now being targeted thru development of specific drugs aimed at different cellular components.

Cell mechanisms of cytokines and interleukins

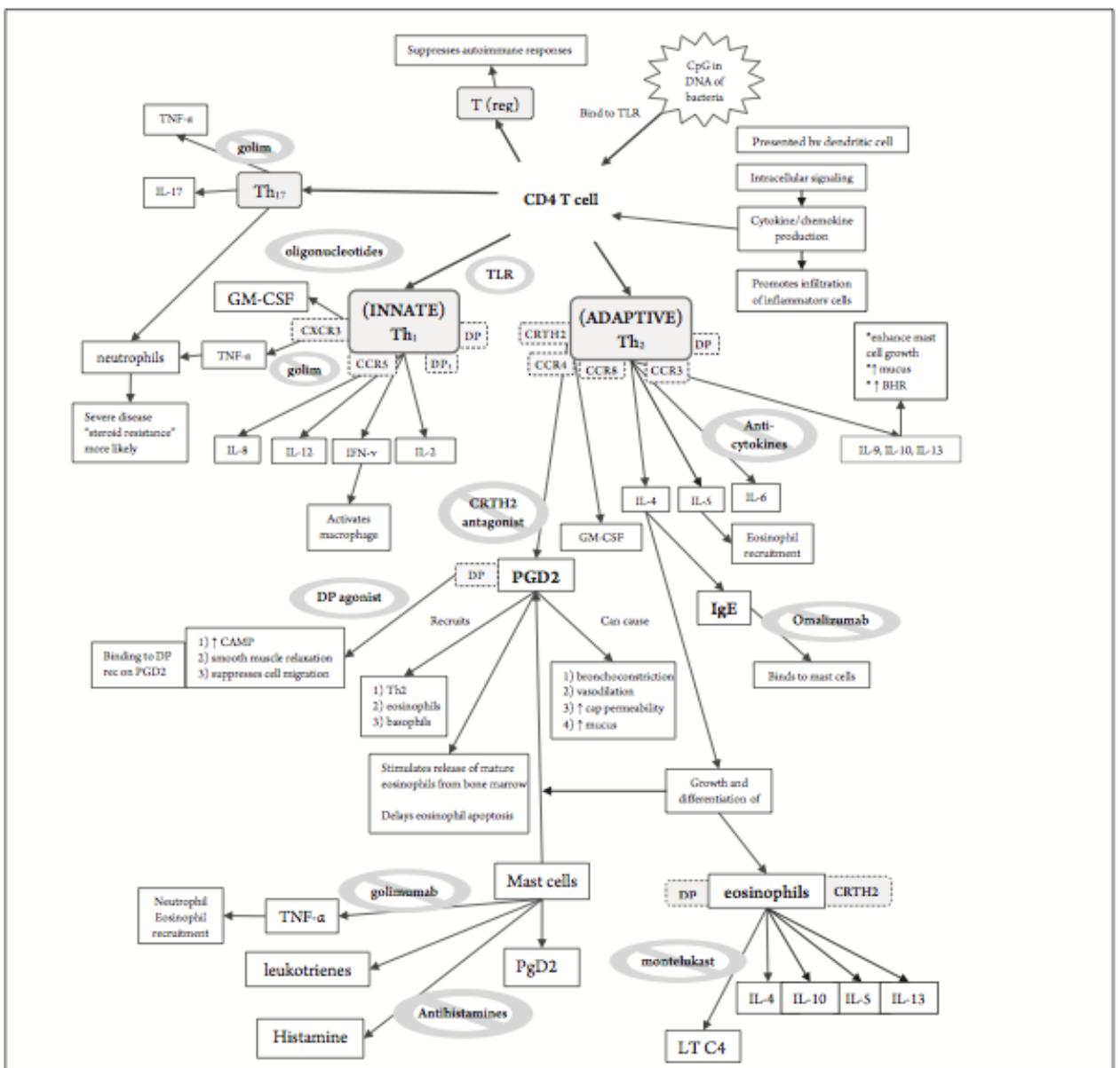

Figure 1-1. The role of existing and emerging therapies in the inflammatory cascade.

Medications targeted to cell functions

- Omalizumab approved in 2003 for moderate to severe asthmatics who have perennial allergies and IgE levels from 30-700. Binds to mast cells to reduce free circulating IgE and thereby reduce allergic reactions upon exposure to allergens. Treatment by injection every 2-4 weeks, response is difficult to predict, trial period of 3-6 months currently recommended.

- Quilizumab is in the experimental phase. 2 short term trials showed reduced allergic response and reduced IgE production after use. Drug is inhaled and may be more convenient to use. Longer term trials with moderate to severe asthmatics must show good efficacy if this is to replace currently available Omalizumab.

Medications targeted to cell functions

- Mepolizumab has undergone a larger scale 32 week trial with moderate to severe asthmatics showing significant improvement in patient outcomes. Study was blinded with patients entered in arms of IV, SubQ, or placebo treatment. Patients on active medication saw significant reduction in exacerbations and circulating eosinophil counts and improved quality of life. This medication blocks IL-5 reducing Eosinophil counts. Upon stopping this medication patients saw an increase in exacerbations and eosinophil counts to pre-treatment levels

Asthma Articles in 2014

- Pregnant women who smoke and those that have second hand smoke exposure during pregnancy have higher risk of having children with asthma
  - Recommended strategy is to intensify smoking cessation and ETS cessation in pregnant women homes.

- Exhaled nitric oxide fraction (FENO) is associated with severity of pediatric acute asthma exacerbations
  - Findings indicate that increasing FENO levels may be associated with decrease in FEV1 and increased symptom severity scores during acute asthma episodes, but more studies are needed to fully understand the implications and parameters of changing FENO levels.

Asthma Articles in 2014

- Adolescents with asthma: are we doing enough?
- Adolescents infrequently interviewed by provider without parent present.
- Decreases chance of getting accurate history of drug, alcohol and smoking use.
  - Recommendation that allergists should enhance their efforts to obtain info on smoking, alcohol and drug use in adolescents, particularly directly with them.

- Sleep duration, sleep hygiene, and insomnia in adolescents with asthma
- Severe asthmatics have significantly more severe insomnia, poorer sleep hygiene, and more daytime sleepiness.
  - Recommendation is to ask adolescents about sleep patterns in order to institute sleep education program interventions if needed.

Asthma Articles in 2014

- Fluticasone furoate-Vilanterol (FF-VI) compared to Fluticasone Furoate (FF) & Placebo (PLBO) in asthma: a randomized trial

- Findings: Once daily FF-VI and FF improve lung function significantly better than placebo but no significant difference found between active drugs.

- Impact: Both FF-VI and FF are effective once daily in asthma care.

Asthma Articles in 2014

- Real-time asthma outreach reduces excessive short acting B2 agonist use: A randomized study

- 1999 asthmatics ages 12-56 with prior ICS and excess SABA use (7 or more canisters in 12 months)
- 1001 patients randomized to intervention group, 998 patients control group: Intervention group received Patient letter recommending ICS use due to excess SABA use, Physician message noting patients uncontrolled asthma status with management recommendations, EMR message to contact patient for an appointment
- Findings: 7th SABA dispensed later, risk ratio lower, allergist visit sooner
- Impact: Proof of concept of effectiveness of linking real time information technology to interventions to improve asthma care.

Asthma Articles in 2014

- Alcohol induced respiratory symptoms (AIRS) are common in patients with aspirin exacerbated respiratory disease (AERD)
- 213 patients with AERD, ASA tolerant asthma (ATA), Chronic rhinosinusitis (CRS), and healthy controls (HP) given questionaire about alcohol induced respiratory symptoms.
- Outcomes: Frequency of upper and lower respiratory symptoms with alcohol consumption
- Findings: Majority of AERD patients experience AIRS which is more severe.
- Impact: HX of AIRS should increase suspicion of AERD both to help in its diagnosis and guide in its avoidance.
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Asthma Articles in 2014

- Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. (Known as single inhaler therapy SIT, or Single Maintenance and Reliever Therapy SMART).
- 4 trials evaluated, 3 trials had patients with severe asthma, 1 trial patients had mild asthma.
- Conclusions: SiT reduces the number of people having asthma exacerbations requiring oral steroids, hospitalization or ER visits compared with fixed dose combination inhalers. Mean daily dose of ICS in SiT was always lower than in the 2 inhaler use groups.
- Findings: This suggests that flexibility in steroid use with SiT might be more effective than a standard fixed dose combination by increasing the dose only when needed and keeping it low during stable stages of asthma.

Asthma Articles in 2014

- A multicenter observational study of U.S. adults with acute asthma: Who are the frequent U.S. ED users?
- 1890 enrolled patients, 863 patients had 1 or more (frequent) ED visits in the past year.
- Among frequent ED users guideline based care was suboptimal.
- Of patients with 6 or more ED visits 85% lacked evidence of prior evaluation by asthma specialist and 43% were not treated with ICS.
- Predictors of frequent ED visits were public insurance, no insurance, and markers for chronic asthma severity (Frequency of ED visits, Hospitalizations, Hx of intubation, depressions, panic-fear, # of meds, OCS use, Nocturnal SX, PFT's)
- Conclusion: This study showed that amongst frequent ED users there is suboptimal management in this high risk population. Future reductions in asthma morbidity and associated health care utilization will require efforts to bridge these major gaps in asthma care.

Allergy and its impact on asthma

- Practice parameters – Documents that establish boundaries for appropriate patient care. They promote consistency in practice to aid clinicians make diagnosis and treatment decisions based on best available scientific evidence and clinical consensus.

- Recent parameters include:
  - ED diagnosis and treatment of anaphylaxis
  - Diagnosis and management of rhinosinusitis
  - Food allergy
  - Management of acute loss of asthma control in the yellow zone
  - Environmental assessment and exposure control of dust mites
  - Environmental assessment and exposure control of cockroaches
  - Environmental assessment and exposure reduction of rodents
  - Environmental assessment and exposure reduction of furry animals

Practice Parameters

- Management of acute loss of asthma control in the yellow zone: a practice parameter, 2014
- Emergency department diagnosis and treatment of anaphylaxis: a practice parameter, 2014
- Food allergy: A practice parameter update – 2014
- Diagnosis and management of rhinosinusitis: a practice parameter update, 2014
- Environmental assessment and exposure control of dust mites: a practice parameter, 2013

Yellow Zone Interventions

- Yellow zone practice parameter is an important step toward reducing exacerbations, improving QOL, and perhaps improving patients perception of their asthma care and their care giver.
- Asthma action plan is used as starting point to make medication changes with increasing asthma symptoms
- Recommends patient directed efforts to initiate increases in medications with increased symptoms
- Recommends patients on ICS consider quadrupling their ICS dose per 24 hours to manage loss of control
- For children under 6 years with recurrent wheezing and risk factors for subsequent asthma consider initiating high dose ICS or oral Montelukast at early signs of wheezing illnesses
- For patients with mild to moderate asthma consider recommending symptom driven use of ICS with inhaled Beta Agonist for control of yellow zone symptoms.
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Allergy and its impact on asthma

- 70-80% of asthmatics have allergic rhinitis
- Reducing allergic exposure means fewer triggers
- Sub Lingual immunotherapy (SLIT) with both drops and tablets has exploded onto the allergy treatment scene in the last 10 years
- House dust mite and grass pollen studies have been done in the US and Europe
- Studies are required for FDA approval and manufacturers are funding those in US and Europe
- Both drops and tablets have shown impressive results during treatment and varying post-treatment periods.
- Asthma rates are reduced in study treatment arms

Allergy and its impact on asthma

- Atopic dermatitis and food allergy practice parameters are particularly interesting as these two allergic diseases potentially forecast the "Allergic March" and a life long history of allergic disease.

- Food allergy, especially peanut allergy is being intensely studied as a "test bed" for understanding the development of the allergic state.

- Atopic dermatitis (eczema) patients have reduced skin barrier function. This may predispose them to food allergy by allowing food particle penetration of the skin barrier and "turning on" the allergic antibody.

Allergy and its impact on asthma

- Peanut allergy is much more prevalent here than in Israel and the far east.
- Exposure to eating peanuts occurs early in life in Israel.
- In the far east, peanuts are typically served raw, boiled or fried.
- In the west, peanuts are typically served roasted or dry roasted. Dry roasting at high temperatures alters peanut protein structure which may be leading to greater allergenicity. Cutaneous contact, especially for those with atopic dermatitis, increases risk of developing allergic sensitivity

Allergy and its impact on asthma

- Late breaking abstract at AAAAI meeting 2/24/15
- Epicutaneous immunotherapy (EPIT) is effective and safe to treat peanut allergy: A multi national double blind placebo controlled randomized phase IIb trial.
- 221 patients with known peanut allergy were randomized to Viaskin Peanut (VP) at 3 different levels or placebo for 1 year trial. Primary efficacy endpoint at 1 year was a peanut protein reacting dose 10 fold greater than entry or post treatment ingestion levels over 1000mg.
- Results: 50% responders at high dose vs. 25% for placebo. Children showed a robust response with high dose EPIT. Dropout for adverse events <1%, no serious adverse events related to treatment.
- Conclusions: In peanut allergy, EPIT appears safe & effective.

Environmental assessment and control

- Practice parameters – Documents that establish boundaries for appropriate patient care. They promote consistency in practice to aid clinicians make diagnosis and treatment decisions based on best available scientific evidence and clinical consensus.
  - Environmental assessment and exposure control of dust mites - 2013
  - Environmental assessment and exposure control of cockroaches - 2013
  - Environmental assessment and exposure reduction of rodents - 2012
  - Environmental assessment and exposure reduction of furry animals - 2012

Teaching techniques and approaches

- Cincinnnatti Children's Hospital Medical Center study found that pharmacies in neighborhoods with high rates of asthma ED use and hospitalization filled fewer asthma controller medications compared to asthma rescue medications.
- Data from 27 Kroger pharmacies in nearby areas calculated "dispensing ratios" of controller meds to rescue meds. Data found that higher controller medication dispensing also meant lower ED and hospitalization rates.
- This study suggested such information could be used to allocate resources to areas in need of improvement thru medication delivery, counseling, or informing physicians regarding patients who do not seem to respond to current therapy.

Factors involved in Non-Adherence GINA 2008

Drug Factors

- Difficulties with inhaler devices
- Awkward regimes (e.g.,four times daily or multiple drugs)
- Side effects
- Cost of medication
- Dislike of medication
- Distant pharmacies

Non-Drug Factors

- Misunderstanding or lack of instruction
- Fears about side-effects
- Dissatisfaction with health care professionals
- Unexpressed/undisclosed fears or concerns
- Inappropriate expectations
- Poor supervision, training, or follow-up
- Anger about condition or its treatment
- Underestimation of severity
- Cultural issues
- Stigmatization
- Forgetfulness or complacency
- Attitudes toward ill health
- Religious issues

Efforts to improve adherence

My Asthma Treatment Goal(s) is/are:

❑ Activities:

_____

_____

_____

❑ Other concerns:

_____

_____

_____

_____

Efforts to improve adherence

The Features of Asthma Medications that matter to me are:

(Rank from 1=most to 4=least important; note specific reasons and concerns)

- ❑ Control over inflammation and symptoms
  - _____
  - _____
  - _____
- ❑ Side effects
  - _____
  - _____
  - _____
- ❑ Cost
  - _____
  - _____
  - _____
- ❑ Convenience
  - _____
  - _____
  - _____

Why make an effort to improve adherence?

- Improved quality of life
- Fewer exacerbations
- Empower patients to self-manage their asthma
- Asthma action plans are underutilized
- Patient adherence is poor
- ICS use is sub-optimal
- Many asthmatics are not well controlled
- Good education and counseling can improve patient outcomes
- Reduce ED visits and hospitalizations
- Reduced health care cost
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Background

- So why is management of acute loss of asthma control so important?
  - If an impending exacerbation is not recognized and treated, it could progress to a severe exacerbation and include ED visit, hospitalization or even death.
  - On the other hand, instructions for patients to take oral steroids and seek medical attention at the first sign of loss of control are likely to result in overtreatment.
  - While the latter might ensure that patients are always treated quickly, such treatment is potentially associated with unnecessary medical intervention and utilization resulting in increased costs, medication side effects with resultant short and long-term morbidity.
  - A targeted approach in which signs of impending exacerbations are recognized early and treated effectively with minimal side effects and disruption to a patient's quality of life would be ideal.

- The chief goal in the management of acute loss of asthma control (yellow zone intervention) is to prevent progression to a full asthma exacerbation ('red zone').
  - The definition of acute loss of asthma control in the yellow zone should distinguish it from occasional asthma symptoms that do not indicate an impending exacerbation (e.g. exercise induced bronchospasm).
  - Since there is generally a narrow window of opportunity for a yellow zone intervention to work, early identification of symptoms and aggressive intervention may optimize the chances for a good outcome.
  - While a 'false' start may lead to the initiation of yellow zone treatment when it may not be needed, the risk of a 'late' start may result in episode progression and the need for treatment with systemic corticosteroids.
    - Rowe Cochrane database of systematic reviews. 2007(3):CD000195.

Adherence to Asthma Controller Therapies

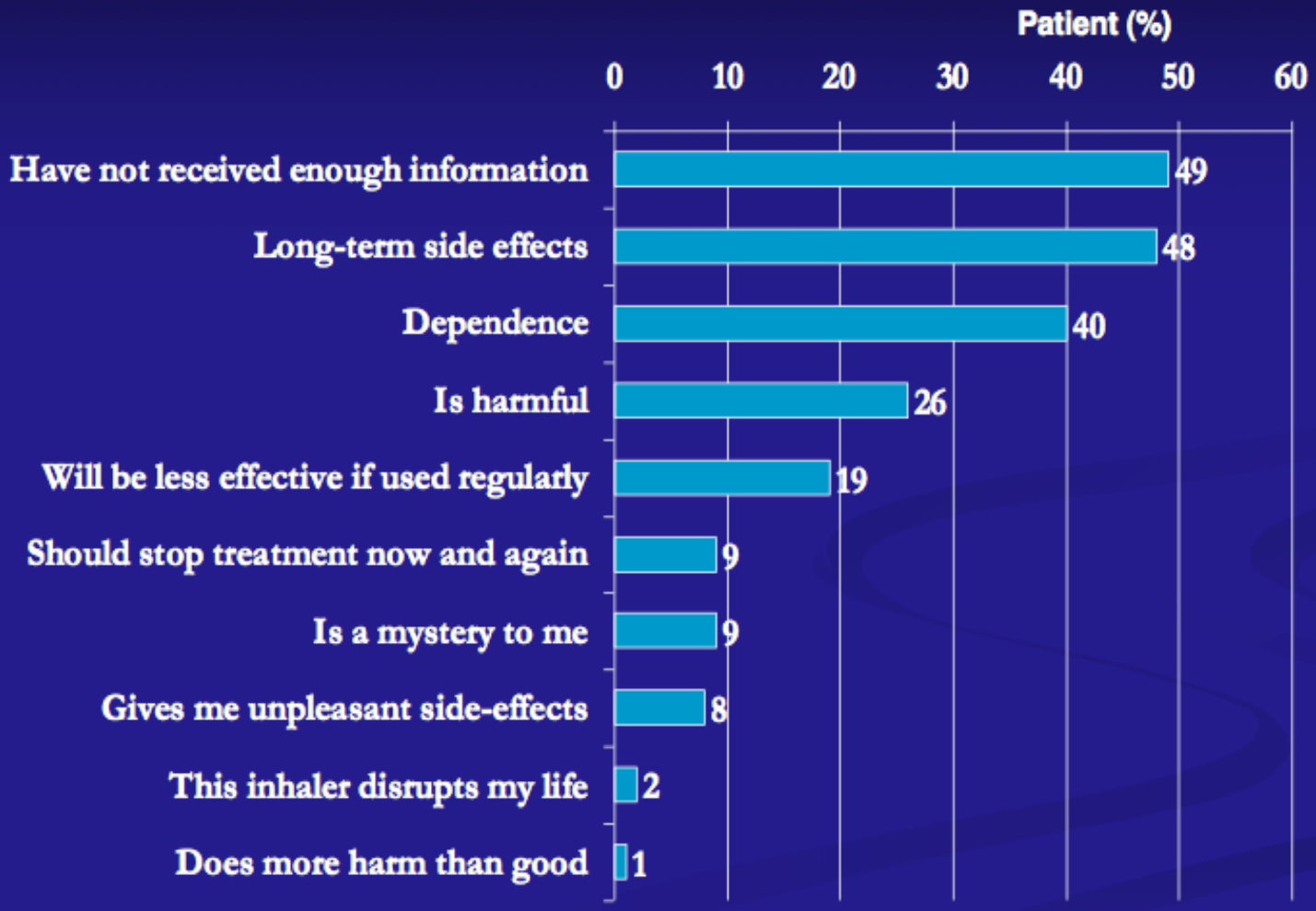
- Overall adherence is ≤70%
  - 6%–44% rate of failure to fill initial prescription[1]
  - ICS used as directed <50% of the time, with range of 0%–98%[2]
  - Reported adherence to LTRAs ranges from 18%–68%[3,4]
- In treatment failures, non-adherence should be considered a possible cause

ICS = Inhaled corticosteroid; LTRA = Leukotriene Receptor Antagonist.

1. World Health Organization 2003. Available at: http://www.who.int/ chronic_conditions/en/adherence_report.pdf. Accessed May 16, 2007. 2. Walders N. *J Pediatr*. 2005;146:177-182. 3. Balkrishnan R. *J Asthma*. 2005;1:35-40. 4. ones C. *J Asthma*. 2003;40:93-101

Multiple Factors Affect Adherence to Asthma Controller Therapies

Patient Concerns with Inhaled Corticosteroids



Horne R. *Chest*. 2006; 130:65-72; Horne R, Weinman J. *Psychol Health*. 2002;17:17-32

Pediatric Asthma Deaths: Mild Patients Are Also at Risk

Robertson et al. Pediatr Pulmonol 1992;13:95-100

If we don't make recommendations to Rx the YZ, patients will on their own!

- Partridge et al. performed structured interviews in 3415 physician-recruited adults aged ≥16 years with asthma to assess:
  - medication use
  - asthma control
  - patients' ability to recognize and self-manage worsening asthma.

Partridge BMC pulmonary medicine. 2006;6:13.

If we don't make recommendations to Rx the YZ, patients will on their own!

Results:

- 88% felt they were "very or quite" confident of their ability to self-manage worsening asthma, without a physician visit.
- 84% had worsening asthma sometime in the past year
- 68% reported being able to identify signs predicting worsening.
- The patients responded to signs of impending worsening by increasing their mediation.

Partridge BMC pulmonary medicine. 2006;6:13.

If we don't make recommendations to Rx the YZ, patients will on their own!

Results:

In general, **patients used a SABA at the onset of symptoms**

- >4-fold increase in SABA inhalations when symptoms were at their peak compared to baseline
- ICS being increased later and to a lesser extent when symptoms were at their worst and often reduced ICS initially.
- When symptoms began to decline, patients reduced intake of both their SABA as well as ICS.
- Only 29% of patients stated that they had been given an acute care plan that including stepping up their maintenance therapy with worsening asthma, 52% acknowledged that they had done so anyway.

- This study clearly demonstrates that patients implicitly are dynamic in their dosing of asthma medications and adjust their medications to match their symptom severity.
- They do so even **without** direction and inappropriately in some cases, reinforcing the importance of a physician developed asthma action plan.

Partridge BMC pulmonary medicine. 2006;6:13.

Daily vs. A-Need CS for Mild Persistent Asthma

- *M*ethods
  - In a double-blind trial, 225 adults (BL FEV-1 approx 88%) underwent randomization.
  - The primary outcome was morning PEF
  - Other outcomes included:
    - FEV1 before and after bronchodilator treatment,
    - the frequency of exacerbations,
    - the degree of asthma control,
    - the number of symptom-free days,
    - quality of life.

Boushey NEJM 2005;352:1519-28

Daily vs. A-Need CS for Mild Persistent Asthma

- **Results**
  - The three treatments produced similar:
    - ↑AM PEF (7.1 to 8.3 percent; 32 liters per minute; P=0.90)
    - rates of asthma exacerbations (P=0.24),
    - intermittent-treatment group took bud, on ave, only 0.5 week of the year.

Boushey NEJM 2005;352:1519-28

Daily vs. A-Need CS for Mild Persistent Asthma

Results

- compared with intermittent therapy or daily zafirlukast therapy, daily budesonide therapy produced greater improvements in:
  - pre-bronchodilator FEV1 (P=0.005),
  - bronchial reactivity (P<0.001),
  - percentage of eosinophils in sputum (P=0.007),
  - exhaled nitric oxide levels (P=0.006),
  - scores for asthma control (P<0.001),
  - number of symptom-free days (P=0.03),
  - No effect on post-bronchodilator FEV1 (P=0.29)
  - No effect on quality of life (P=0.18).

- Daily zafirlukast therapy did not differ significantly from intermittent treatment in any outcome measured.

Boushey NEJM 2005;352:1519-28

Daily vs. A-Need CS for Mild Persistent Asthma

- *Conclusions*
  - It may be possible to treat mild persistent asthma with short, intermittent courses of inhaled or oral corticosteroids taken when symptoms worsen. Further studies are required to determine whether this novel approach to treatment should be recommended.

Boushey NEJM 2005;352:1519-28

Dynamic Dosing

- A strategy termed adjustable maintenance dosing (AMD/SMART), using combination therapy with an ICS and a LABA, has been studied by a number of research groups.

- While the traditional fixed-dose strategy is designed to allow the patients to maintain complete control, the adjustable dosing strategy encourages the patient to escalate extra dosing based on symptoms.
-
- This may enable reduction in cumulative controller dose and avoidance of OCS.

How do we put this all together?

On Demand Therapy

- What is being used in the real world?
- Our patients are demanding it!
- Good evidence it works in mild asthma
- Inferior to regular use in moderate asthma
- Not appropriate for poor perceivers of dyspnea
- We can be certain, more studies are to come